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Rituximab before and during pregnancy

A systematic review, and a case series in MS and NMOSD

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Abstract

Objective

To evaluate the safety of rituximab treatment before and during pregnancy in women with MS and neuromyelitis optica spectrum disorders (NMOSDs) who may be at risk of relapses by performing a systematic literature review combined with a retrospective single-center case series.

Methods

Studies were systematically identified in the PubMed, Google Scholar, and EMBASE using the key terms "pregnancy" and "rituximab"; 22 articles were included for review (>17,000 screened). Then, patients with MS and NMOSD from 1 center (University of California, San Francisco) exposed to rituximab before conception were identified through medical record review.

Results

Systematic review: We identified 102 pregnancies with rituximab use within 6 months of conception: 78 resulted in live births and 12 in spontaneous abortions. Of 54 live births with reported gestational age, 31 occurred at term (37 weeks+) and 2 before 32 weeks. When checked, B-cell counts were low in 39% of newborns and normalized within 6 months. Case series: we identified 11 pregnancies (1 ongoing) in 10 women (7 MS and 3 NMOSD) treated with rituximab within 6 months of conception. All completed pregnancies resulted in term live births of healthy newborns (1 lost to follow-up at term). No maternal relapses occurred before/during pregnancy; 1 occurred postpartum (NMOSD).

Conclusion

No major safety signal was observed with rituximab use within 6 months of conception. Beyond the need for monitoring neonatal B cells, these observations support prospectively monitoring a larger patient cohort to determine whether rituximab may safely protect women with MS and NMOSD who are planning a pregnancy against relapses.

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Glossary

DMT = disease-modifying therapy; **NMOSD** = neuromyelitis optica spectrum disorder.

Women are disproportionately affected by MS and neuromyelitis optica spectrum disorders (NMOSDs), and management of disease-modifying therapies (DMTs) before pregnancy represents an ongoing challenge for neurologists. No safety concerns have been identified with platform injectable DMTs,[1–3] but discontinuation before pregnancy is typically recommended for the more potent oral and infusible DMTs. Therefore, many women may face a heightened risk of relapses during the period between DMT discontinuation and the potentially protective (in MS[4,5] but not in NMOSD[6,7]) effects of pregnancy. This risk could be further magnified by recurrence of severe "rebound" MS disease activity after discontinuing natalizumab[8–12] or fingolimod,[13–16] and in fact these two DMTs appear associated with a higher risk of relapse during pregnancy in the new treatment era.

Rituximab, frequently used off-label for the treatment of MS and NMOSD,[17,18] may offer distinct advantages for managing women at the time of conception. First, its biological effects (B-cell depletion) persist long after the drug is effectively eliminated (typically, 5 maximal half-lives[3] each of 19–22 days or approximately 110 days[19]). These data suggest that women could attempt conception approximately 3.5 months after their last infusion without significant risk of fetal exposure to the monoclonal antibody, while conferring protection against MS flares throughout the pregnancy. In addition, should a woman unintentionally conceive before rituximab elimination, the risk of fetal exposure is low, as IgG1 subclass antibodies are not transferred across the placenta during the first trimester. Finally, transition to rituximab from natalizumab may confer protection against the risk of a rebound of disease activity associated with natalizumab withdrawal.[20]

To date, pregnancy and neonatal outcomes in women with MS and NMOSD treated with rituximab are largely unreported.[3,20] To bridge this gap, we performed a systematic review of the medical literature, combined with a retrospective single-center case series.

Methods

Systematic review

To summarize and analyze the existing literature on pregnancy outcomes in women treated with rituximab for any indication within 6 months of conception through delivery, we performed a systematic review.

Data sources

Original research studies were identified from the PubMed/MEDLINE, EMBASE, and Google Scholar databases. The search terms "pregnancy" and "rituximab" were used in combination to include all articles with the key words for all years (last updated July 3, 2017). Further hand searching of reference lists of obtained articles was performed.

Study selection

This search yielded over 17,000 results; titles and abstracts were screened for relevance, and relevant manuscripts underwent subsequent review. Studies were excluded if they were not written in English, were reviews with no specific individual- or cohort-level data, or if mothers were exposed to rituximab more than 6 months before conception (list of citations available upon request). Twenty-two publications were included in the current review, with 102 mothers exposed to rituximab in the desired timeline (see Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram,[21] figure).

Data extraction and analysis

Data were extracted (G.D.) and checked (R.B.) for individual-level information relating to maternal and fetal outcomes. Most articles were case reports, a few were retrospective, and 1 was a meta-analysis of a database; none included control groups.

Retrospective single-center case series

Sample selection

To identify a cohort of women with MS or NMOSD treated with rituximab within 6 months of conception or during delivery at the University of California, San Francisco (UCSF) Multiple Sclerosis and Neuroinflammation Center, we performed search of relevant medical records. Among 323 patients with CNS inflammatory disorders who treated with rituximab between August 2010 and July 2017, we identified 160 women who received rituximab infusions before the age of 50 years. Their medical records were manually reviewed to identify pregnancies occurring within 6 months of exposure to rituximab. We identified 10 women with at least 1 pregnancy occurring within the selected timeframe. These were cross-referenced with participating clinicians' individual caseloads.

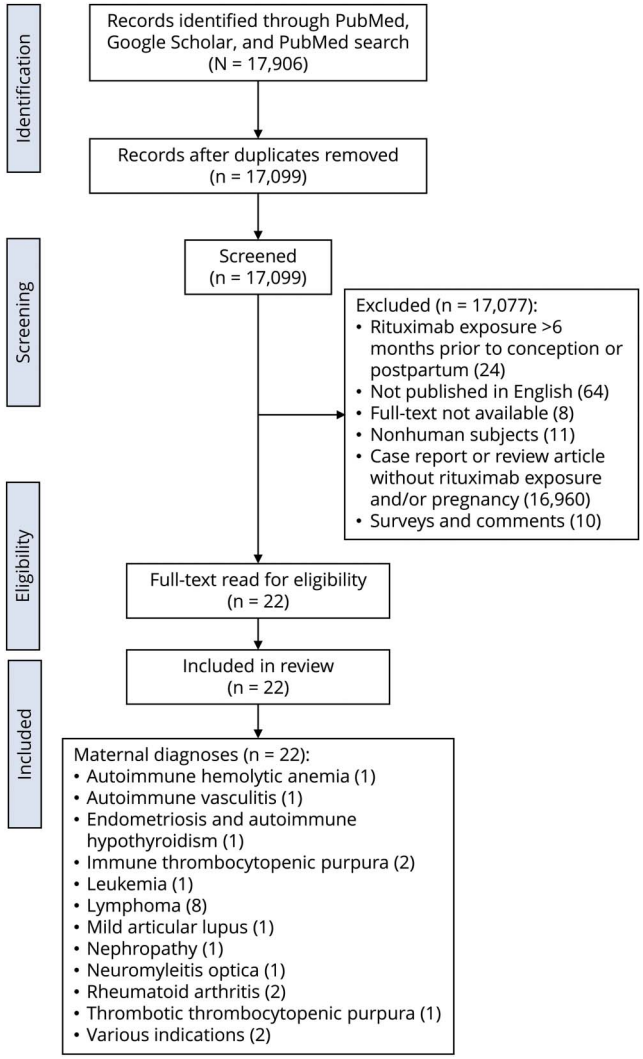
Data collection

Medical records were reviewed to record pregnancy outcomes (delivery or fetal loss), maternal MS or NMOSD disease activity during pregnancy and postpartum (relapses, symptoms, and medications), maternal pregnancy-related and other complications (e.g., preeclampsia), and neonatal outcomes (gestational age, delivery mode, and newborn health status).

Standard protocol approvals, registrations, and patient consents

The UCSF Committee of Human Research approved the study protocol for retrospective analysis of electronic medical record–derived MS data with no patient contact (Ref #13-11686).

Figure Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic review



Results

Systematic review

We identified 102 women who became pregnant within 6 months of exposure to rituximab or who were treated with rituximab while pregnant. Of these 102 patients, 38 were described in case reports or small case series, and 64 were described in a meta-analysis[22] (table 1). Medical indications for rituximab treatment included 2 cases with NMOSD, as well as lymphoma, rheumatoid arthritis, and immune-mediated thrombocytopenic purpura, among others. Many mothers experienced successful medical management for their primary condition with rituximab.

A total of 74 of the 102 pregnancies reported resulted in live births. In the 41 pregnancies from the case reports and case series, 1 fetal demise was reported at 21 weeks of gestation in a patient with a history of miscarriages[23] and 1 stillbirth was reported at 27 weeks of gestation due to placental insufficiency.[24] There was also 1 therapeutic abortion and 1 spontaneous abortion in a patient taking methotrexate until confirmation of pregnancy.[24] In the larger meta-analysis of the global drug safety database investigating fetal outcomes in patients with rituximab exposure (64 pregnancies with 1 ongoing at the time of publication), 11 spontaneous abortions were reported, as well as 15 medical abortions.[22] These mothers were often taking other medications, including methotrexate, an antifolate drug that is often used to treat ectopic pregnancies.

Newborns were delivered at term (37 weeks of gestational age or after) in 31 of the 54 live births, where gestational age was reported. None of the deliveries were severely preterm (less than 28 weeks of gestation, according to the World Health Organization guidelines), and 2 were born before 32 weeks. One mother on an rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone regimen for lymphoma underwent emergency cesarean section at 34 weeks due to fetal distress. The baby was born with a patent ductus arteriosus that was fixed the day after birth.[25] Besides, the patent ductus arteriosus, the only other newborn physical abnormalities or medical conditions reported involved twins: one was born with a clubfoot and the other with erythema toxicum neonatorum. Both twins developed normally and did not have any complications.[26]

Neonatal B-cell depletion was found in 9 of the 23 pregnancies in which B-cell counts were measured and reported. None of these neonates experienced any infectious complications, and none were noted to experience any adverse reactions to vaccinations. All B-cell levels normalized within 6 months, some sooner.

Retrospective single-center case series

We identified a total of 11 pregnancies from 10 patients who became pregnant within 6 months of rituximab exposure (table 2): 6 with MS and 3 with NMOSD, with pregnancy ongoing in 1 patient at the time of data collection. No patients received rituximab infusions while pregnant. No patients experienced relapses between rituximab treatment and conception.

Medical complications arose in 4 of the 10 completed pregnancies and included pregnancy-related (gestational diabetes, pre-eclampsia with postpartum eclampsia) and disease-related (blurring of vision and lightheadedness at about 5 months of gestation and worsening spasticity; numbness in fingertips 2 weeks before delivery); neither of the disease-related complications was determined by the treating neurologist to represent a clinical relapse, and neither required additional medications or hospitalizations.

Of the 10 completed pregnancies, 9 resulted in term live births, with healthy children (status unknown for 1 as the mother moved out of the area and closer to familial supports for delivery). Most mothers breastfed for at least a few weeks

Table 1 Systematic review of 22 articles reporting maternal and fetal outcomes for 102 pregnancies characterized by maternal treatment with rituximab within 6 months of conception or during pregnancy

Citation	N = mothers; n = neonates	Maternal diagnosis	Timing of rituximab exposure	Comedications	Maternal perinatal course	Neonatal outcomes			Additional complications
						Gestational age at delivery	B-cell or immunoglobulin depletion	Malformations and other complications	
Maternal malignancy indications									
Azim et al.[35]	N = 7; n = 7	Lymphoma: 6 NHL, 1 relapsing follicular	NHL: 2nd trimester; relapsing follicular: 1st trimester	Patients with NHL also received chemotherapy	NR	NR	Low B-cell count in 3/7, all normalized within 6 mo	NR	NR
Burnette et al.[36]	N = 1; n = 1	Primary CNS lymphoma	3rd trimester	Dexamethasone	NR*	31 wk via C-section	Low B-cell count stabilized by 4-mo follow-up	None	None
Daver et al.[37]	N = 1; n = 1	Hairy cell leukemia	3rd trimester	Prednisolone and cladribine	Blood counts improved significantly	40 wk	NR	None	NR
Decker et al.[38]	N = 1; n = 1	DLBCL	2nd trimester	Metoclopramide for nausea and vomiting	NR	33 wk	Low B-cell count normalized within 3 mo	None	None
Kimby et al.[39]	N = 1; n = 1	DLBCL	Preconception and 1st trimester	NR	Tumor progression, treated; patient in partial remission	40 wk via vaginal delivery	Low B-cell count normalized by 5 wk postpartum	None	None
Lee et al.[25]	N = 1; n = 1	DLBCL	2nd to 3rd trimesters	Part of R-CHOP regimen	Received remaining cycles of R-CHOP postpartum; remission by 13-mo follow-up	34 wk via C-section for fetal distress	NR	Patent ductus arteriosus closed after birth	NR
Mandal et al.[40]	N = 1; n = 1	DLBCL	2nd to 3rd trimesters	Part of R-CHOP regimen	Complete remission	37 wk via C-section	Low B-cell count and Ig levels, normalized within 6 mo	None	None
Perez et al.[41]	N = 1; n = 1	Primary mediastinal large B-cell lymphoma	2nd to 3rd trimesters	Part of R-CHOP regimen	Complete resolution of mediastinal mass postpartum	34 wk	NR	None	None
Rey et al.[42]	N = 1; n = 1	DLBCL	During pregnancy	Part of R-CHOP regimen	Partial remission; treated with 2 more cycles of R-CHOP	33 wk	NR	None	None

Continued

Table 1 Systematic review of 22 articles reporting maternal and fetal outcomes for 102 pregnancies characterized by maternal treatment with rituximab within 6 months of conception or during pregnancy *(continued)*

Citation	N = mothers; n = neonates	Maternal diagnosis	Timing of rituximab exposure	Comedications	Maternal perinatal course	Neonatal outcomes			Additional complications
						Gestational age at delivery	B-cell or immunoglobulin depletion	Malformations and other complications	
Mixed maternal indications									
Chakravarty et al.[22]	43 (clinical trials); 21 (RTX with established pregnancy); N = 64; n = 37; 1 ongoing at the time of publication	Various indications: lymphoma, RA, SLE, ITP, MS, TTP, and Castleman disease	Range from 6 mo preconception through 3rd trimester	Many, including cyclophosphamide, vincristine, doxorubicin, methotrexate, oral contraceptives, corticosteroids, azathioprine, fondaparinux, and anti-infectives	NR	From 35 to 41 wk	NR	NR	SAB*: 11; TAB*: 15; all SABs and TABs with comedications
Maternal autoimmune disease indications									
Abisror et al.[23]	N = 1; n = 0	Mild articular lupus; history of fetal loss	1st/2nd trimester (12-wk gestation)	Hydroxychloroquine, low-dose aspirin, prednisone, low-molecular-weight heparin, monthly IVIG	Hyperemesis gravidarum	Fetal demise at 21 wk	NR	NR	NR
Al-Rabadi et al.[43]	N = 1; n = 1	Primary membranous nephropathy and circulating anti-PLA2R antibodies	Few weeks preconception	Lisinopril, warfarin, and simvastatin; all discontinued at week 6 of pregnancy	Persistent postpartum proteinuria, retreatment with RTX	38 wk via C-section	NR	None	None
De Cock et al.[24]	N = 8; n = 10	Rheumatoid arthritis	Within 6 mo preconception	Methotrexate, sulfasalazine, hydroxychloroquine, corticosteroids, azathioprine, and ciclosporin	Throat infection, chest infection, and 1 patient with 3 urinary tract infections	NR	NR	NR	Stillbirth: 1, 27 wk due to placental insufficiency; SAB: 1; used MTX until pregnancy confirmed; TAB: 1; 1 lost to follow-up
Gall B et al.[44]	N = 1; n = 1	ITP	3rd trimester	Corticosteroids, IVIG, and splenectomy	Platelet counts rose to normal	NR	Low B-cell count normalized by 4-mo follow-up	None	None
Laliberte et al.[45]	N = 4; n = 5	Autoimmune vasculitis	Within 3 mo preconception	Azathioprine, cyclophosphamide, and prednisone	Patients on prednisone developed gestational diabetes	31–41 wk	Normal in 3 of 3 that were measured	NR	NR
Mariampillai et al.[46]	N = 1; n = 1	TTP	3rd trimester	Decadron	Platelet levels improved	36 wk via C-section	NR	None	NR

Continued

Table 1 Systematic review of 22 articles reporting maternal and fetal outcomes for 102 pregnancies characterized by maternal treatment with rituximab within 6 months of conception or during pregnancy *(continued)*

Citation	N = mothers; n = neonates	Maternal diagnosis	Timing of rituximab exposure	Comedications	Maternal perinatal course	Neonatal outcomes			Additional complications
						Gestational age at delivery	B-cell or immunoglobulin depletion	Malformations and other complications	
Martínez-Martínez et al.[47]	N = 1; n = 1	ITP	2nd/3rd trimester	Methylprednisolone and azathioprine	NR	34 wk	Low B-cell count normalized within 3 mo	None	None
Ng et al.[48]	N = 1; n = 1	Endometriosis, autoimmune hypothyroidism; previous failed IVF	6 mo before successful IVF	Thyroxine for hypothyroidism; IVF treatment with LMWH, aspirin, steroids, and IVIG	Gestational diabetes managed by diet	39 wk	NR	None	None
Ojeda-Uribe et al.[49]	N = 1; n = 1	Autoimmune hemolytic anemia	1st trimester	Initially corticosteroids and packed RBC transfusions, but with poor compliance, R was introduced; corticosteroids continued at lower dose	NR	38 wk	NR	None	None
Ojeda-Uribe et al.[50]	N = 2; n = 2	(1) RA and (2) idiopathic TTP	(1) 6 mo preconception and 1st trimester. (2) 9 wk preconception	(1) Methotrexate	NR	(1) 38 wk via C-section and (2) 39 wk via vaginal delivery	(1) was doing well at 1- and 6-mo follow-up, and (2) normal B-cell counts; doing well at 1- and 6-mo follow-up	None	None
Pellkofer et al.[51]	N = 1; n = 1	NMOSD	1 wk preconception	Azathioprine discontinued before rituximab infusions	Relapse 10 d postpartum, treated with corticosteroids; then RTX after second relapse; stable since then	NR	Normal B cell counts	None	None
Ton et al.[26]	N = 1; n = 2	RA	6 wk preconception	Prior use of unspecified DMARD monotherapy and combination with TNF-alpha blockers	Improvement with RTX	37 wk, twins	Normal B-cell counts in both twins	Twin 1: clubfoot; twin 2: erythema toxicum neonatorum	None

Abbreviations: AHA = autoimmune hemolytic anemia; DLBCL = diffuse large B-cell lymphoma; DMARD = disease-modifying antirheumatic drug; ITP = immune-mediated thrombocytopenic purpura; IVF = in vitro fertilization; IVIG = IV immunoglobulin; LMWH = low-molecular-weight heparin; MTX = methotrexate; NMOSD = neuromyelitis optica spectrum disorder; NHL = non-Hodgkin lymphoma; NR = not reported; RA = rheumatoid arthritis; RBC = red blood cell; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; RTX = rituximab; SAB = spontaneous abortion; SLE = systemic lupus erythematosus; TAB = therapeutic abortion; TTP = thrombotic thrombocytopenic purpura.

Table 2 Pregnancy and neonatal characteristics in 11 pregnancies characterized by maternal exposure to rituximab for treatment of demyelinating diseases within 6 months of conception: a single-center case series

		Maternal status at conception						Delivery			
Patient	Diagnosis	Age (y)	Disease duration (y)	EDSS (within 6 mo of conception)	DMT before RTX	Time between RTX infusion and conception	Maternal complications during pregnancy	Complications	Gestational age	Apgar scores	Mother's postpartum course (and follow-up time)
1	NMOSD	36	6	1.5	Interferon	3 mo	None	None	Term (40w2d)	6 and 9	Radiologically confirmed relapse 3 mo postpartum, restarted RTX 1 mo after relapse; clinically stable at 12 mo (12+ mo)
2	MS	32	4	2.5	Glatiramer acetate	1 mo	None	None	Term (38w1d)	8 and 9	No new symptoms; exclusively breastfed for 8 mo before restarting RTX (12+ mo)
		34	6	2.5		1 mo	Chronic productive cough for 2 mo before delivery	Eclampsia while inpatient after delivery	Term (40w3d)	9 and 9	Readmitted for seizure after discharge and 3-d course of IVIG; postpartum depression; currently breastfeeding with plans to restart RTX when done (3 mo)
3	NMOSD	32	4	4	Mycophenolate mofetil	2 mo	None	None	Term (38w0d)	NR	Breastfed for 3 weeks before restarting RTX; no rebound relapses, but did have some right orbital pain at 5 mo (12 + mo)
4	MS	23	6	3	Fingolimod	6 mo	2.5-mo gestation: lightheaded, fell with no damage to fetus; 2 wk before delivery: numbness at fingertips	None	Term (39w4d)	NR	No relapses; restarted RTX 5 mo postpartum; depression and anxiety at 12 mo (12+ mo)
5	MS	34	3	2	Glatiramer acetate	4 mo	Gestational diabetes managed with diet and exercise	None	Term (40w3d)	NR	No relapses; breastfed for 6 mo with monthly steroids; stable at 12 mo (12+ mo)
6	MS	29	11	2.5	Fingolimod	5 mo	None	None	Term (40w0d)	NR	Clinically and radiologically stable; breastfed for 10 mo postpartum; received ocrelizumab infusion at 11 mo (12+ mo)
7	MS	26	7	3	Fingolimod	3 mo	NR	NR	Term (NR)	NR	No postpartum relapses; did not breastfeed; received RTX within 1 mo after delivery (12+ mo)

Continued

Table 2 Pregnancy and neonatal characteristics in 11 pregnancies characterized by maternal exposure to rituximab for treatment of demyelinating diseases within 6 months of conception: a single-center case series *(continued)*

Patient	Diagnosis	Maternal status at conception			DMT before RTX	Time between RTX infusion and conception	Maternal complications during pregnancy	Delivery			Mother's postpartum course (and follow-up time)
		Age (y)	Disease duration (y)	EDSS (within 6 mo of conception)				Complications	Gestational age	Apgar scores	
8	NMOSD	37	3	4	None	2 mo	None	NR	Term (38w3d)	NR	Moved out of area for delivery and transferred care at the time of delivery
9	MS	31	2.5	5	Fingolimod	2 mo	None	None	Term (41w5d)	8 and 9	Received steroids postpartum (immediately postpartum at the time of submission)
10	MS	32	10	1.5	Tecfidera	2 mo	None to date to pregnancy ongoing	—	Pregnancy ongoing (4 mo)	—	—

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IVIG = IV immunoglobulin; NR = not reported; NMOSD = neuromyelitis optica spectrum disorder; RTX = rituximab.
Term pregnancy = 37 weeks of gestational age or after.

before restarting treatment. One patient of the 8 with data for the full-year postpartum, who carried an NMOSD diagnosis, relapsed postpartum.

Discussion

Rituximab, which seems to reduce relapse frequency in both MS and NMOSD, may offer significant advantages for women with MS and NMOSD who are planning a pregnancy and require ongoing DMT, given that its biological effect extends significantly beyond its pharmacokinetic half-life. Although individual variability exists in terms of the exact half-life of rituximab,[27] or of any administered monoclonal antibody, an estimate of effective elimination would require 5 maximal half-lives[3] each of 19–22 days or approximately 110 days.[19] B-cell repletion occurs in most individuals within 8 months, but in the phase 2 study of rituximab, MS disease activity remained suppressed 1 year after a single course of treatment. However, not enough is known about pregnancy outcomes in women with MS and NMOSD who conceive after rituximab treatment to fully understand the risks and advantages of this approach.

In the current systematic review of pregnancy outcomes in women with a number of medical conditions treated with rituximab (some with severe diseases and using other concomitant medications), we calculated an overall reported rate of spontaneous abortions of 12%, and 41% of reported deliveries occurred before 37 weeks (2 before 32 weeks). Three malformations or medical conditions were reported among the 67 newborns (as a point of reference from the general population in the United States, the rate of major malformations at birth is 3%[28]). The primary adverse effect noted was a low neonatal B-cell count in 39% of the newborns evaluated that normalized within 6 months in all cases. Of interest, in 1 patient with NMOSD whose last treatment with 100 mg rituximab was 7 months before conception, a low B-cell percentage detected in fetal cord blood suggested that maternal rituximab treatment might influence fetal B-cell counts even after rituximab should have been completely eliminated from the maternal circulation.[21]

Limitations of this literature review include the retrospective nature and small size of the cases series and reports, potential under-reporting, and lack on information on potential confounders. For example, the coexisting use of glucocorticoids, antimetabolites, and other chemotherapy agents could potentially confound any causal role attributed to rituximab for these adverse events. Furthermore, there was little information on other possible confounding variables such as obstetrical or clinical disease histories, which could also influence the pregnancy course and outcome. Prospective evaluation of pregnancy outcomes, including case-control studies evaluating the rates of pregnancy loss or prematurity, as well as longer term information about children's immunologic trajectories, is required to overcome the current

limitations and biases. Nonetheless, this review did not identify major concerns that would preclude treatment with rituximab within 6 months of conception in women with demyelinating diseases at risk of inflammatory activity when discontinuing other MS medications before conception.

Next, in our preliminary case series of 11 pregnancies in women with demyelinating diseases treated with rituximab within 6 months of conception, none of the patients experienced a relapse before conception or during pregnancy. Those with completed pregnancies did not experience major rebound activity after delivery; only 1 patient (NMOSD) experienced a postpartum relapse (up to 1/3 women with MS have been reported to relapse postpartum). Most of the treated patients breastfed for at least a few weeks before receiving another dose of rituximab. All children were reported to be healthy at birth and to remain healthy at follow-up.

Limitations from the current case series include the small sample size and possible bias if some pregnancies in women not receiving primary or obstetrical care in the same hospital system as our tertiary care center were not captured in the patient's medical record. However, given the complex medical decision making that typically happens at the time of conception and delivery in women with demyelinating diseases, it is likely that we identified most of the pregnancies within our rituximab-treated cohort. Furthermore, to date, regular B-cell monitoring in the mother during and after pregnancy and in the neonate has not been routinely performed in our clinic. As decreased neonatal B-cell counts were noted in the systematic review, this information would provide additional insights into the effect of rituximab intrapartum and postpartum and would allow optimization of the timing of rituximab treatment. Finally, there were no patients in our single-center case series who received rituximab during pregnancy, limiting discussion of possible effects of intrapartum maternal treatment and fetal exposure.

Currently, to treat women with demyelinating diseases during pregnancy, glatiramer acetate can be used before, and even during, pregnancy; but some therapies commonly used in MS are relatively contraindicated.[29] Fingolimod, dimethyl fumarate, and teriflunomide are small molecules that could cross the placenta and potentially cause birth defects. Natalizumab treatment during pregnancy may be associated with neonatal pancytopenia,[30] and natalizumab treatment discontinuation can be associated with recurrence of severe MS disease activity.[31] For example, in a retrospective study evaluating 22 pregnancies after discontinuation of natalizumab, recurrence of disease activity was noted in 95.5% of the cases, despite little to no activity in the year before natalizumab discontinuation.[32] Disease activity seemed more limited when conception occurred shortly after or even before discontinuation of natalizumab, with recurrence of disease activity often occurring 4–6 months after discontinuation. To our knowledge, no data on daclizumab use during pregnancy are available in humans. Like rituximab, alemtuzumab has a pharmacodynamic effect that is far longer than its pharmacokinetic half-life and theoretically could be used in women with MS who are planning pregnancy. However, alemtuzumab-treated patients are at high risk for treatment-related, de novo thyroid and other autoimmune diseases. Because maternal autoantibodies can be transmitted across the placental barrier and thereby can cause disease in the fetus or newborn, treatment with alemtuzumab before pregnancy must be approached with caution. In March 2017, ocrelizumab, a humanized monoclonal anti-CD20 antibody, was approved by the US Food and Drug Administration for both relapsing and progressive MS.[33] Its average half-life is 26 days—possibly shortening the preconception therapeutic window relative to rituximab. In an initial report of 9 women whose embryo/fetus was considered "exposed" to ocrelizumab (i.e., here, infusion within 3 months of conception) during the MS clinical trials, pregnancy outcomes included 1 healthy term baby, 6 elective terminations, and 2 ongoing pregnancies.[34] Therefore, an unmet need for effective treatments for women living with MS and NMOSD who are considering pregnancy remains.

While awaiting prospective pregnancy and postpartum monitoring, the current systematic review and case series provide some preliminary reassurance that rituximab may offer a window of time before conception during which inflammatory activity can be mitigated, without evidence of major adverse effects during pregnancy. Longer term follow-up and a larger sample size are needed to determine the safety of rituximab before and during pregnancy in women with MS and NMOSD, and independent studies will be required to assess the potential benefits and risks of other B-cell depleting agents such as ocrelizumab in this situation.

Author contributions

Study concept and design: G.D., J.M.G., B.A.C.C., and R.B. Statistical analysis and interpretation of data: G.D. and R.B. Acquisition of data and interpretation of results: G.D., V.D., L.D., and R.B. Manuscript drafting and revision: G.D., V.D., J.M.G., C.B., B.A.C.C., L.D., A.G., S.H., and R.B.

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Allergan. C. Bevan reports no disclosures. B.A.C. Cree served as an editor of *Annals of Neurology*; consulted for AbbVie, Biogen, EMD Serono, GeNeuro, Novartis, and Sanofi-Genzyme; and received research support from Acorda, Celgene, Hoffman-LaRoche, MedImmune, Novartis, and Teva. L. Do reports no disclosures. A. Green served on the scientific advisory board of MedImmune, Novartis, Inception 5 Biosciences, and Bionure; served on the editorial board of *JAMA Neurology* and *Neurology*; holds a patent for Remyelination molecules and pathways; consulted for Inception 5 Sciences; received research support from Novartis Pharma OCTIMS, Inception Sciences, the NINDS, the NIA, the National MS Society, the Sherak Foundation, and the Hilton Foundation; and served as an expert witness of Mylan Pharma vs Teva Pharma. S. Hauser served on the scientific advisory board of Symbiotix, Annexon, Bionure, and Molecular Stethoscope; serves on the board of trustees of Neurona; received travel funding and speaker honoraria from F. Hoffman La Roche; receives publishing royalties from the McGraw-Hill Education, provided writing support for F. Hoffman La Roche; received research support from the NIH, National MS Society, and Conrad N. Hilton Foundation. R. Bove served on the scientific advisory board of Roche-Genentech, Sanofi-Genzyme, and Novartis; received gifts from the Sherak Foundation and Akili; has a patent pending for Selective estrogen receptor modulators and remyelination; and received research support from the California Initiative to Advance Precision Medicine, National MS Society, and Hilton Foundation. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

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